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09/485,245	03/27/2000	ALISON HOPKINS	28911/36128	1697

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MARSHALL O'TOOLE GERSTEIN  
MURRAY & BORUN  
6300 SEARS TOWER  
233 SOUTH WACKER DRIVE  
CHICAGO, IL 60606-6402

EXAMINER

WILDER, CYNTHIA B

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1637

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**BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES**

Application Number: 09/485,245  
Filing Date: March 27, 2000  
Appellant(s): HOPKINS, ALISON

\_\_\_\_\_  
Jeffrey Sharp  
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed September 12, 2005 appealing from the Office action mailed July 12, 2004.

**(1) Real Party in Interest**

A statement identifying by name the real party in interest is contained in the brief.

**(2) Related Appeals and Interferences**

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

**(3) Status of Claims**

The statement of the status of claims contained in the brief is correct.

**(4) Status of Amendments After Final**

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

**(5) Summary of Claimed Subject Matter**

The summary of claimed subject matter contained in the brief is deficient. 37 CFR 41.37(c)(1)(v) requires the summary of claimed subject matter to include: (1) a concise explanation of the subject matter defined in each of the independent claims involved in the appeal, referring to the specification by page and line number, and to the drawing, if any, by reference characters and (2) for each independent claim involved in the appeal and for each dependent claim argued separately, every means plus function and step plus function as permitted by 35 U.S.C. 112, sixth paragraph, must be identified and the structure, material, or acts described in the specification as corresponding to each claimed function must be set forth with reference to the specification by page and line number, and to the drawing, if any, by reference characters.

The brief is deficient because the summary states, "the independent claims 7 and 11 provides method of forming random mixtures of dried oligonucleotides which are resistant to self annealing (see page 3, lines 12-27 of the specification; see also page 8, Table, 7<sup>th</sup> column)".

A review of the specification at page 3, lines 12-17, finds that the specification makes no

mention of a random mixture of dried oligonucleotides 6-mer to 8-mer being resistant to self-annealing. A review of the specification at page 8, Table, 7<sup>th</sup> column does not show a random mixture of dried oligonucleotides 6-mer to 8-mer being resistant to self-annealing, but rather shows that there is a reduction in self-annealing when the random mixture of dried oligonucleotides 6-mer to 8-mer are utilized as a labeling composition. Again, nothing on the cited pages recites a method of forming random mixtures of dried oligonucleotides which are resistant to self annealing. Consequently, the summary incorrectly states an element which is not expressly stated or depicted in the specification.

#### **(6) Grounds of Rejection to be Reviewed on Appeal**

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct, though appellant's characterizations regarding the examination are not correct. Additionally, the following changes have been made: The rejections under 35 USC 112 second paragraph for indefiniteness directed to claims 7-10 are not presented for review on appeal because they have been withdrawn by the Examiner based upon further review of the claim language.

#### **(7) Claims Appendix**

The copy of the appealed claims contained in the Appendix to the brief is correct.

#### **(8) Evidence Relied Upon**

5,759,804	GODISKA et al	6-1998
EP 0 726 310	SHEN et al	02-1996

**(9) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims:

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 7-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Godiska et al. (5,759,804, filed November 17, 1993) in view of Shen et al. (EP 0 726 310 A1 February 09, 1996). Regarding claims 7-14, Godiska et al teach a method comprising a random mixture of oligonucleotides which are 6-mers, wherein the composition further contains at least a supply of nucleotides for chain extension, a labeled nucleotide, and a polymerase enzyme (col. 8, lines 27-31). Godiska et al differs from the instant invention in that Godiska et al do not expressly teach wherein the solution comprising the random mixture of 6-mers is in a freeze-dried state. Shen et al teach a method and composition similar to that of Godiska et al, wherein said composition is present in a dry state (page 4, lines 37-41). Shen et al teach wherein the composition may comprise primers, a polymerase enzyme, a supply of nucleotides for chain extension, and a stabilizer (page 6, lines 3-7 and 22). Shen et al teach that the composition present in the dry state is advantageous because the composition is stable for a prolonged period, even when stored at high temperature. Shen et al further teach that a composition in a dried state is useful in shipping and storage of commercial preparations for use in e.g., nucleic acid amplification kits

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(page 6, lines 39-41). Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have been motivated to have provided the random mixture of 6-mers in the method as taught by Godiska et al in a dried state for the advantage taught by Shen et al that a nucleic acid composition (such as primers) present in a dried state is useful in shipping and storage of commercial preparations due its increase stability, even when stored for prolonged periods or when stored at high temperatures.

***Claim Rejections - 35 USC § 112 first paragraph: New Matter***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to a method of forming a random mixture of oligonucleotides which is resistant to self-annealing comprising the steps of selecting a random mixture of oligonucleotides which are 6-mers to 8-mer and drying said mixture. Applicant provides no cited support for the new limitation "oligonucleotides which is resistant" and thus a review of the specification as originally filed does not support or depict what is claimed. While the specification illustrates as a group a reduction in the percent (%) of self-priming when utilizing mixtures of oligonucleotides which are 6-mer to 8mers versus oligonucleotides which are 9-

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mers, there is no disclosure which illustrates whether or not the reduction in % of self-priming is due to a "selection process" of oligonucleotides having a self annealing resistant property or whether or not the reduction in % self-priming is due to an interaction between the random oligonucleotides or whether or not the reduction in the % of self priming is due the sequences of the oligonucleotides. No support has been found anywhere in the specification which suggests that the oligonucleotides of the invention are "resistant" to self-priming or "resistant" to self-annealing. Therefore, the specification would not have suggested to the skilled artisan that the Applicant was in possession of the claimed invention as of filing date.

#### **(10) Response to Argument**

##### **Issues**

**1. The rejection of claims 7-14 under 35 USC 103(A) over Godiska and Shen should be reversed because the law does not require that claim elements teach the achievement of unexpected results or suggest the desirability of an applicant's solution to a problem.**

##### **Issue 1-103(a) Rejection**

**A.** Appellant alleges that specifically the rejection should be reversed because the Examiner applied an incorrect legal standard in maintaining an obviousness rejection by requiring that the claims recited "limitations...that would suggest that such [unexpected] results were achieved" (Office Action of 7/12/04 at page 5, lines 14-15), when the applicant had demonstrated unexpected results over the prior art. Appellant states that the Examiner erroneously rejected the claims when she asserted that the claims did not "recited any features which would suggest the desirability" of the inventor's solution to a problem facing the art (Office Action 7/12/04 at

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pages lines 10-12). Appellant alleges that there are no requirements that claim elements teach the achievements of unexpected results or suggest the desirability of an applicants' solution to a problem.

Appellant alleges that the present invention relates to the art of recombinant DNA synthesis and uses of random primer kits to rapidly synthesize and efficiently synthesize DNA. Appellant alleges that random primers are short segments of DNA that consist of essentially every possible combination of nucleotide bases for a given length. Appellant states that they are often used to carry out DNA syntheses when the sequence of a particular gene may not be known and specific primers for that gene are therefore unavailable. Appellant asserts that workers select random primer collections of various lengths (e.g., 6-mers, 10-mers, 15-mers), but the primers themselves are random for a selected length.

Appellant alleges that various kits containing liquid solutions of oligonucleotides were known in the prior art for practice of random priming methods (Stratagene). Appellant alleges that while short, randomly, generated nucleotide primers in solution (e.g., liquid 6-mers) were provided in these kits, there had been a trend in the art of DNA synthesis toward using liquid solutions of longer primers in order to provide more rapid priming (e.g., Megaprime and Ready-to-Go kits). Appellant alleges that other commercially available kits in the art provided dried primer kits such as dried 15-17 mers (e.g. Rediprimer, EP 298-269) or dried 48- and 22-mers (Shen, EP 0 726 310). Appellant alleges that long, dried primers were preferred to short dried primers because of the belief that such longer primers would provide more rapid priming than shorter primers.



Appellant alleges that the present invention relates to the discovery that long dried primers frequently bind to themselves, i.e., self-anneal or self-prime, rather than to the DNA to be synthesized. Appellant alleges that the Applicant has discovered that short (6-8 mers) dried primers unexpectedly resist self-annealing and provide improvements in activity and labeling intensity compared with longer dried primers. Appellant alleges that specially Examples 2 and 4 demonstrate this activity and labeling intensity between short dried 6-8-mers which resist self-annealing compared with longer long dried 9-mers (and above) then used in the art. Appellant alleges that the applications of Examples demonstrate a critical and unexpected difference in self-priming activity and labeling intensity between 6-8 mers and 9- mers and there is no suggestion in the art that such different could occur. Appellant argues that according the obviousness rejection under 35 USC 103(a) should be reversed because Godiska and Shen fail to teach the desirability of short primers (6-8 mers) in a dried primer system or that 6-8 mers would behave differently with respect to self-priming activity and labeling intensity than do 9-mers. Appellant alleges that more specifically, Godiska discloses liquid 6-mers but fails to teach that the selection of 6-mers constitutes a critical range or that short primers (6-8 mers) would be desirable in a dried primer system. Appellant alleges that while Godiska discloses random mixtures of 6-mers and other ingredients, the Examiner acknowledged that Godiska does not teach a labeling composition in a dried state. Appellant states that there is nothing in Godiska that teaches that selection of 6-mers to 8-mers is important in either a liquid states to reduce self-annealing.

Applicant states that in addition, Shen discloses dried 48-mers and 22-mers but fails to suggest that such dried primers should be shorten, or alternatively any reasons why the short

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primers of Godiska should be dried. Appellant alleges that this is because the prior art generally taught that longer primers were preferred because longer primers have higher melting temperature and are thus more specific. Appellant argues that while the Examiner does not dispute the unexpected results demonstrated in the application, she asserts that the claims are unpatentable because the claims do not recited the unexpected results or suggest the desirability of Applicant's solution to the problem of self-annealing. Appellant summarizes *In re Chupp, Carter-Wallace, Inc. v. Otte* and *In re Mechant* and alleges that because the Examiner has applied an improper legal standard, that the claims recite "limitations that would suggest that such [unexpected] results were achieved" and that the claims "recite features which would suggest the desirability" of the invention's solution to a problem, the rejection should be reversed.

In response, the Examiner asserts that Appellant has taken the Examiner's arguments of the Office action of 7/12/04 out of context because the Office action of 7/12/04 at page 5, lines 15-16 summarizes the Examiner viewpoint that the **"the claims do not describe the steps or characteristics, which distinguishes them from the prior art"**. The Examiner has not applied an improper legal standard but rather maintains that the claims as broadly written do not describe or recite any steps or characteristics which distinguishes Applicant's invention over the teachings of the prior art. The Examiner agrees with Appellant that the art teaches the use of random primers collections of various lengths in random priming methods and the use of dried primer kits that contained long primers, such as dried 15-17-mers. However, the examiner disagrees that the instant invention, specifically the Examples 2 and 4 demonstrates a critical difference in self-priming activity and labeling intensity between short dried 6-8 mers which resist self-

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annealing compared with longer long dried 9-mers and above. In fact, contrary to Applicant arguments, the specification specifically the examples 2 and 3 do not depict any resistance of self-annealing when using primers 6-8 mers in DNA labeling experiments but rather shows a reduction in self-annealing (self-priming). The Example 2 at page 9 of the specification depicts "DNA labeling with dCTP-<sup>32</sup>P". The results show at week 3, the percent incorporation of dCTP-<sup>32</sup>P when using the 9-mer was at 61.9%, whereas the percent incorporation of dCTP-<sup>32</sup>P when using the 6-mer was 69.6%. The percent of reduction in self priming at 3 weeks when using the 9-mer was 17.5%, whereas, the percent of self-priming when using the 6-mer was 9.7%, showing about a 55% reduction in self annealing, not a total resistance of self annealing when using the 6-mer over the 9-mer in the labeling experiment. At 6 weeks, the results show the percent incorporation of dCTP-<sup>32</sup>P when using the 9-mer was at 71.4%, whereas the percent incorporation of dCTP-<sup>32</sup>P when using the 6-mer was 80.8%. The percent of reduction in self priming at 6 weeks when using the 9-mer was 18.0 %, whereas, the percent of self-priming when using the 6-mer was 8.4%, showing about a 46.6% reduction in self annealing, not a total resistance of self annealing when using the 6-mer over the 9-mer in the labeling experiment. At 10, weeks, the percent incorporation of dCTP-<sup>32</sup>P when using the 9-mer was at 65.8%, whereas the percent incorporation of dCTP-<sup>32</sup>P when using the 6-mer was 75.0%. The percent of reduction in self priming at 10 weeks when using the 9-mer was 20.2%, whereas, the percent of self-priming when using the 6-mer was 11.9 %, showing about a 58.9% reduction in self annealing, not a total resistance of self annealing when using the 6-mer over the 9-mer in the labeling experiment. The experiments were repeated for up to 25 weeks and none of the results at 16, 21 or 25 weeks show a complete resistance to self-annealing but rather show a

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reduction in self- annealing when using 6-mers in a dried state rather than 9-mers (see Example 2).

The Example 3 depicts the percent incorporation of 6-mer primers taken from the average of two reactions versus the percent incorporation of 9-mer primers taken from a single experiment. The percent incorporation was measured using primer concentrations in the reaction from 1.0 to 6.0 O.D./ml for each reaction. The results show that the molar concentration needs to increase as the primer length is reduced. The specification specifically states that "the results obtained in the Example 3 were obtained using wet reagents", but *speculates* that "the conclusion would apply also when dried primers are used" (see specification page 10, lines 8-9). Again, the Example 3 does not depict any resistance to self-annealing or self-priming as argued by Appellant and additionally does not show the use of any random hexamer versus nanomer in a dried state.

**B.** In response to Appellants arguments against the references of Godiska and Shen individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, the primary reference of Godiska et al., is cited for its teaching of a method comprising a random mixture of 6-mers oligonucleotide as required by the claims 6, 10, 11 and 14 and reagents for a chain extension assay as required by claims 9 and 13. As stated in the prior Office action of 7/12/04, Godiska et al do not expressly teach wherein the 6-mers are in a dried state. However, this limitation is provided in the teachings of the secondary reference by Shen. Shen et al teach a method and composition comprising primers in a dried state and reagents for

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chain extension as required by claims 7-8, 11 and 12. Shen provides motivation for providing the primer and other reagents required for chain extension in a dry state. Shen et al teach that a composition, comprising primers and reagents in a dried state is advantageous because the composition is stable for a prolonged period, even when stored at high temperature. Shen et al further teach that a composition in a dried state is useful in shipping and storage of commercial preparations for use in e.g., nucleic acid amplification kits (page 6, lines 39-41). Thus, the combined teaching of Godiska et al in view of Shen et al establishes a case of obviousness over the instant invention. MPEP 8<sup>th</sup> edition states that "[T]he test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference....Rather, the test is what the combined teaching of those references would have suggested to those of ordinary skill in the art " *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981). See also *In re Sneed*, 710 F.2d 1544, 1550, 218 USPQ 385, 389 (Fed. Cir. 1983) ("[I]t is not necessary that the inventions of the references be physically combinable to render obvious the invention under review."); and *In re Nievelt*, 482 F.2d 965, 179 USPQ 224, 226 (CCPA 1973) ("Combining the teachings of references does not involve an ability to combine their specific structures").

C. Finally, in response to Applicant's arguments that the Examiner asserts that the claims are unpatentable because the claims do not recite the unexpected results or suggest the desirability of Applicant's solution to the problem of self-annealing, it is again noted ~~noted~~ that the context of the Examiner's arguments have been mischaracterized. Rather, the Examiner stated that "unexpected results as indicted by Applicant must correlate with the invention provided in the specification". While the claims broadly recite a method of forming a random mixture of

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oligonucleotides which is resistant to self-annealing as recited in the claims 7-10, the specification on the other hand, illustrates a reduction in the percentage of self-priming (self-annealing) when utilizing oligonucleotides 6-mers versus 9-mers, but does not illustrate a resistance to self-annealing by selecting a mixture of said oligonucleotides. The examiner further stated that "the claims do not describe any steps or characteristics or improvements, which distinguishes them from the prior art." Accordingly, Appellant's arguments are not persuasive.

#### **Issue 2-New Matter**

**2. The rejection of claims 7-10 under 35 USC 112 first paragraph - written description, should be reversed.**

A. Appellant asserts that the rejections on the basis that the application lacks written descriptive support for the recitation of "oligonucleotides which are resistant to self-annealing" should be reversed because those of ordinary skill in the art would recognize that the dried 6-mer to 8-mer oligonucleotide mixtures were resistant to self-annealing and self priming as demonstrated in Examples 2 and 4. Appellant asserts and those skill in the art recognize, that self-priming and self-annealing are the same phenomenon (see page 3, lines 12-27 of the specification where both terms are used). Appellant asserts that the Examiner acknowledges "a reduction in the percentage of self-priming when utilizing oligonucleotide 6-mers to 8-mers versus 9-mers (Office action of 7/12/04, page 7, lines 1-2). Appellant states that as such a worker of ordinary skill would appreciate that the primers of the invention, which are resistant to self-priming as acknowledged by the Examiner, are resistant to self- annealing. Appellant states that the rejection on the gases that there is no disclosure which illustrates whether or nor

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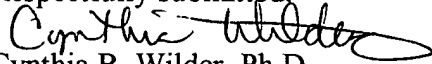
the rejection in % of self-priming is due to a selection process (Office action of 7/12/04 at page 8, lines 7-8) should be reversed because the unexpected results of the invention do not result from a selection of primers having particular sequences. Applicant states as discussed above, and as recognized by those of ordinary skill, Applicant's primers are random, meaning that they comprise essentially all sequence for a given length. Appellant states that the unexpected properties of the primers result because they are short (6-mers to 8-mers) and dried. Appellant asserts that Applicant describes the invention throughout the disclosure and teaches the practice of the invention in a manner such that those of ordinary skill in the art would recognize that Applicant was in possession of the invention claimed. Applicant summarizes *In re Koller* and *In re Barker* and asserts that no reasons have been set forth why one of ordinary skill would not believe that Applicant was in possession of the originally claimed invention at the time of filing.

B. In response, once again Appellant has taken the Examiner's arguments out of context. Contrary to Appellants arguments, the Examiner did acknowledge the primers of the invention being resistant to self-priming, rather the Examiner acknowledged a "reduction" in the percent of self-priming or self-annealing when using the primers of the inventions that are 6-mer to 8-mer versus 9-mer. The Examiner maintains that the specification does not recite or depict "any resistance" to self-annealing or "resistance" to self-priming. Likewise, the specification does not describe or disclosed any properties or characteristics of the primers that would suggest to those skill in the art or those of ordinary skill art that the oligonucleotides as claimed have any "resistance properties". Therefore, the Examiner maintains that the neither the specification nor claims support a method of forming a random mixture of oligonucleotides which is resistant to self-annealing as claimed. Accordingly, Appellant's arguments are not persuasive.

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For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

  
Cynthia B. Wilder, Ph.D.

Examiner

Art Unit 1637

Conferees:

Gary Benzion

SPE, Art Unit 1637

Gary Jones

SPE, Art Unit 1634


MARSHALL, GERSTEIN & BORUN LLP

6300 Sears Tower

233 South Wacker Drive

Chicago, Illinois 60606

  
GARY BENZION, PH.D.  
SUPERVISORY PATENT EXAMINER  
TECHNOLOGY CENTER 1600

  
W. Gary Jones  
Supervisory Patent Examiner  
Technology Center 1600